Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
P03-0032PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/005253	13.04.2004	18.04.2003

International Patent Classification (IPC) or national classification and IPC

Applicant

JAPAN SCIENCE AND TECHNOLOGY AGENCY

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☒ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      1 disk , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005253

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-26 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-11 received by this Authority on 30.09.2004

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets fig. 1-5 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, nos. 12-14

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	5-11	YES
	Claims	1-4	NO
Inventive step (IS)	Claims		YES
	Claims	1-11	NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: JP 10-33087 A (Koichi TANAKA), 10 February 1998, entire text (Family: none)

Document 2: T. HARADA et al., "Functions of the two glutamate transporters GLAST and GLT-1 in the retina," Proc. Natl. Acad. Sci. USA., (1998), Vol. 95, No. 8, pages 4663 to 4666

Document 3: WO 03/28444 A1 (Japan Science and Technology Corp.), 08 April 2003, entire text

Document 4: JP 2002-369639 A (The Institute of Physical and Chemical Research), 24 December 2002, entire text

Document 5: WO 02/08415 A1 (Japan Science and Technology Corp.), 31 January 2002, entire text

Document 6: C. K. YORWERK et al., "Depression of retinal glutamate transporter function leads to elevated intravitreal glutamate levels and ganglion cell death," Invest Ophthalmol. Vis. Sci. (2000), Vol. 41, No. 11, pages 3615 to 3621

Document 7: Makoto NIIKE, "Ryokunaisho no Shin Chiryoho -Rinsho ni Oyo Kano na Gan'atsu Kako, Kyokusho Junkan Kaizen oyobi Shinkei Hogoyaku no Kaihatsu-," (2002), Heisei 11 to

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

13 Nendo Kagaku Kenkyuhi Hojokin (Kiban Kenkyu (A) (I)) Kenkyu Seika Hokokusho, entire text (in particular, refer to page 5)

The inventions set forth in claims 1 to 4 lack novelty and do not involve an inventive step in the light of documents 1 to 2 cited in the international search report.

Documents 1 to 2 present knockout mice that exhibit decreased GLAST functions. In particular, document 2 discloses the feature of creating chimeric mice by means of ES cells from which the GluT-1 (GLAST) gene has been deleted and then mating the resulting chimeric mice with C57BL/6 mice; furthermore, document 2 also discloses the feature of inserting a neomycin-resistant gene into exon 6 of the GLAST gene when deleting the GLAST gene.

Documents 1 to 2 do not make any disclosure in relation to the intraocular pressure or the retinal ganglion cells in the GLAST knockout mice; however, document 8 indicates that if the antisense oligonucleotide of the GLAST gene is introduced into a mouse, then the resulting mouse will exhibit a decrease in the number of retinal ganglion cells present therein, and the like. As a result, it is likely that mice which lack the GLAST gene will exhibit a normal intraocular pressure and a decrease in the number of retinal ganglion cells present therein; therefore, the inventions that are set forth in claims 1 to 4 cannot be differentiated from the knockout mice of the inventions that are disclosed in documents 1 to 2.

The inventions set forth in claims 6 to 8 do not involve an inventive step in the light of documents 1 to

5 cited in the international search report.

The technical feature of backcrossing genetically modified mice with pure line mice five times or more when creating knockout mice or transgenic mice in order to more closely replicate the genetic background of a pure line mouse is considered to have been well known prior to the priority date of the present application, as disclosed in documents 3 to 5, for example; therefore, in the light of the abovementioned well-known technical feature, it would have been easy for a person skilled in the art to conceive of repeatedly backcrossing the knockout mice with wild mice five times or more in order to purify the knockout mice in the inventions that are disclosed in documents 1 to 2.

The inventions set forth in claims 5 and 9 to 11 do not involve an inventive step in the light of documents 1 to 2 and 6 to 7 cited in the international search report.

Document 6 indicates that if the antisense oligonucleotide of the GLAST gene is introduced into a mouse, then the resulting mouse will exhibit a decrease in the number of retinal ganglion cells present therein.

In addition, document 7 suggests the possibility that pathways leading directly to the cell death of retinal ganglion cells, such as the damage to retinal ganglion cells that is associated with an increase in the concentration of a neurotoxin such as extracellular glutamine, may contribute to normal tension glaucoma.

Therefore, it would be easy for a person skilled in the art to conceive of attempting to use the GLAST gene knockout mice from the inventions that are disclosed in documents 1 to 2 as animal models for normal tension glaucoma, which is a disease that is caused and primarily

characterized by a decrease in the number of retinal ganglion cells, as well as to conceive of using said knockout mice from the inventions that are disclosed in documents 1 to 2 in order to screen for compounds that are useful for the prevention and/or the treatment of normal tension glaucoma in the light of the disclosures in documents 6 to 7.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*